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10/725,965	12/02/2003	Erik Buntinx	29248/18	2844

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/725,965	BUNTINX, ERIK	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41,42,79,81,82 and 84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41,42,79,81,82 and 84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/12/2009, 5/18/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner notes the receipt of the amendments and remarks received in the office on 5/18/2009 amending claims 41, 42, 79, 81, 82, 84. Claims 1-40, 43-78, 80, 83, 85 have been canceled. Claims 41, 42, 79, 81, 82, 84 are pending and are being examined on the merits herein.

Response to Remarks

Applicants' arguments regarding the rejection of claims 41, 78, 79 under 35 U.S.C. 102(b) as being anticipated by Wirz-Justice et al. (Applicant cited IDS reference: Alzheimer disease and associated disorders, 14(4), 212-215), claims 41, 42, 78, 79, 81-84 under 35 U.S.C. 112, first paragraph, Claims 81-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, Claims 41, 42 and 80 under 35 U.S.C. 103(a) as being unpatentable over Dudley et al. (US 2004/002482, effective filing date Mar 15 2002) in view of Wirz-Justice et al. (Applicant cited IDS reference: Alzheimer disease and associated disorders, 14(4), 212-215) and Medicaments and Psychotropes (Applicant cited IDS reference) have been fully considered and the rejections are withdrawn due to the amendment of claims. Applicants' amendments necessitated the new and modified rejections presented below. Accordingly, the action is made Final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 81-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 81 has a limitation " wherein pipamperone and the selective serotonin reuptake inhibitor are the sole pharmaceutically active ingredients in the composition" is new matter and does not have support in the specification. The specification teach a pharmaceutical composition 'containing' (para 009, abstract) or a pharmaceutical composition 'comprising' (para 011, claims 41, 42) and in para 0078 teach "to prepare the pharmaceutical compositions, comprising the compounds or the combination of the first and second compound described herein, an effective amount of the active ingredients, in acid or base addition salt form or base form, is combined in admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration". The specification does not teach anywhere including examples, a composition comprising pipamperone and the selective serotonin reuptake inhibitor are the sole pharmaceutically active ingredients. Applicants' state in the arguments that support for the amendments to Claim 81 can be found at least in Claim 82, and in the application as filed at least on page 5, line 4, the paragraph spanning pages 15-16, Example 2 on page 17, and Table 2 on page 20. Claim 81 had a consisting limitation (which was rejected under New matter in the previous rejection) and had the limitations pipamperone as the active ingredient and citalopram as the

active ingredient. Nowhere in the claim there is a limitation of pipamperone and the selective serotonin reuptake inhibitor are the sole pharmaceutically active ingredients. Page 5, line 4 of the specification teach the dose of pipamperone, 5-15 mg. Paragraph spanning pages 15-16 in specification state "to prepare the pharmaceutical compositions, comprising the compounds or the combination of the first and second compound described herein, an effective amount of the active ingredients, in acid or base addition salt form or base form, is combined in admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration". Example 2, page 17 shows a combination therapy results (administration of citalopram and pipamperone separately and not in a pharmaceutical composition). Accordingly, the limitation of "wherein pipamperone and the selective serotonin reuptake inhibitor are the sole pharmaceutically active ingredients in the composition" is new matter and does not have support in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 41, 42, 80, 81, 82, 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wirz-Justice et al. (Applicant cited IDS reference: Alzheimer disease and associated disorders, 14(4), 212-215), Medicaments and Psychotropes (Applicant cited IDS reference).and Dudley et al. (US 2004/002482, effective filing date Mar 15 2002).

Wirz-Justice teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml (Table 1, p 214).

Medicaments and Psychotropes document teaches that an initial dose of 10 mg dipiperon can be administered.

Dudley et al. teach combinations and compositions for treating or preventing or reducing the risk of developing a depressive disorder (a mood disorder) or the symptoms associated with the disorder comprising compounds such as citalopram, pipamperone (see abstract, para 0132, lines 14 and 42). Dudley et al. teach citalopram and pipamperone as antidepressants (para 0132). The reference teach that the combinations of the antidepressant agents can be used in the methods, kits, combination and compositions (para 0132, p 10, lines 5-7).

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a composition comprising both the compounds pipamperone and citalopram in the same composition because Wirz-Justice teaches combination therapy

comprising citalopram and pipamperone and Dudley suggest the composition and combination of the compounds and further teach the compounds are useful as antidepressant agents. One of ordinary skill in the art would have been motivated to incorporate the agents herein in a single combination pharmaceutical composition because combining the agents herein each of which is known to be useful to treat mental disorders including depression individually into a single composition useful for the very same purpose is *prima facie* obvious. See *In re Kerkhoven* 205 USPQ 1069. One of ordinary skill in the art at the time of the invention would have been motivated to formulate such a composition in expectation of success as well to achieve synergistic and or additive benefits from deriving such a formulation as both the compounds are taught to be useful as antidepressant agents. Please note that the recitation of "intended use", e.g., treating a mood disorder or an anxiety disorder does not lend patentable weight to composition claims. The intended use of the composition and a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a composition comprising such compounds in an amount range as claimed in claim 41 because Wirz-Justice teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml, Medicaments and Psychotropes document teaches that an initial dose of 10 mg dipiperon can be administered. Also, the amount of an ingredient in a composition is

clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of applicant's invention.

Claims 81-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wirz-Justice et al. (Applicant cited IDS reference: Alzheimer disease and associated disorders, 14(4), 212-215) and Medicaments and Psychotropes (Applicant cited IDS reference).and Bymaster et al. (Applicant cited IDS reference: WO 98/11897).

Wirz-Justice et al teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml (Table 1, p 214).

Medicaments and Psychotropes document teaches that an initial dose of 10 mg dipiperon can be administered

Bymaster et al. teaches a pharmaceutical composition comprising a first component an antipsychotic and a second compound a serotonin reuptake inhibitor. The reference for example, teaches a risperidone/fluoxetine pharmaceutical composition (p 6) as a combination and teaches several examples of combinations of various antipsychotic and serotonin reuptake inhibitor compounds (See examples). The reference further teach that the antipsychotic agents while improving the lives of

psychotic patients immeasurably, may not be sufficient to treat every psychotic patient as psychotic conditions appear to have a complex etiology, some schizophrenics which exhibit depressive episodes or depressed individuals which also have psychotic episodes may not find total relief using only one atypical psychotic agent (p 1, lines 25-30). The reference teaches that the adjunctive therapy of antipsychotic agent with a serotonin reuptake inhibitor provides a potentiation of the increase in the concentration of norepinephrine observed as an effect of administration of a first component compound by administration of a second component compound (p 24, lines 1-5). The reference further teaches the adjunctive combination of an antipsychotic and a serotonin reuptake inhibitor may be administered as a single pharmaceutical composition and such compositions may take any physical form which is pharmaceutically acceptable and such adjunctive pharmaceutical compositions contain an effective amount of each of the compound (p 16, lines 33-37, p 17, lines 1-5) and also teaches addition of pharmaceutically acceptable carriers and inert materials in the formulation (p 17-18, formulations 1-8).

Wirz-Justice et al teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml (Table 1, p 214).

Medicaments and Psychotropes document teaches that an initial dose of 10 mg dipiperon can be administered

It would have been obvious to one of ordinary skill in the art at the time of the invention to have formulated a pharmaceutical composition comprising pipamperone, an antipsychotic agent and a serotonin reuptake inhibitor from the teachings of Wirz Justice

et al. and Bymaster et al. Bymaster et al. reference teaches a pharmaceutical composition consisting of antipsychotic agents with serotonin reuptake inhibitors (e.g citalopram). The reference further teach that the antipsychotic agents while improving the lives of psychotic patients immeasurably, may not be sufficient to treat every psychotic patient as psychotic conditions appear to have a complex etiology, some schizophrenics which exhibit depressive episodes or depressed individuals which also have psychotic episodes may not find total relief using only one atypical psychotic agent. The reference teaches that the adjunctive therapy of antipsychotic agent with a serotonin reuptake inhibitor provides a potentiation of the increase in the concentration of norepinephrine observed as an effect of administration of a first component compound by administration of a second component compound. Thus Bymaster et al. teaches the benefits of formulating a composition comprising an anti-psychotic agent and an antidepressant as the sole active ingredients and further teach making such formulations (formulations 1-8). One having ordinary skill in the art would have been motivated to formulate a pharmaceutical composition comprising citalopram, an anti-depressant agent and pipamperone, a known anti-psychotic drug as the sole active agents in expectation of achieving success in formulating such composition and in providing improved therapeutic benefits by increasing the concentration of norepinephrine as an effect of administration of an anti-psychotic component compound by administration of a second component compound (SSRI). Please note that the recitation of "intended use", e.g., treating a mood disorder or an anxiety disorder does not lend patentable weight to composition claims. The intended use of the composition

and a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate a composition comprising such compounds in an amount range as claimed in claim 41 because Wirz-Justice teaches combination medication of pipamperone 20-30mg/ml and citalopram 10 mg/ml, Medicaments and Psychotropes document teaches that an initial dose of 10 mg dipiperon can be administered. Also, the amount of an ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of ingredient to add in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of ingredient amount would have been obvious at the time of applicant's invention.

Response to Arguments

Applicants' arguments regarding the dose effective of pipamperone has been fully considered. Applicants' argue that low dose of pipamperone has not been used in the prior art and the prior art teaches to use the highest tolerable dose for treating psychoses, synergy of low dose of pipamperone and SSRI's and the present invention does not involve a mere optimization of dosage by routine experimentation. In

response, Applicants' claim a composition comprising pipamperone in an amount of 5-15 mg and a selective serotonin reuptake inhibitor. Applicants' in the argument state that "The inventor surprisingly found that at the claimed daily low dose, pipamperone has a specific, but double effect, i.e. a high selective D4 and 5-HT2A receptor antagonistic effect. As such, pipamperone can exert its augmenting effect on the second, SSRI compound. This effect has not been described in the prior art, nor is there any hint towards such an effect. This daily low dose of pipamperone has not been used in the prior art" (p 8 of 19). In response, Applicants' show by example in a combination therapy administration of 4 mg of pipamperone composition and 10mg of citalopram composition. The claims are broad with respect to the SSRI inhibitors and the amounts in the composition. The claim is for a composition comprising pipamperone in an amount of 5-15 mg and any SSRI inhibitor with any amount. However Applicants' have shown an effect of 4 mg pipamperone with 10 mg of citalopram in combination therapy, in which the drugs are administered separately and only for single dose of pipamperone and single dose of citalopram. There are no examples of making formulations comprising pipamperone with any of the SSRI's or administration of such formulations (with low dose pipamperone as claimed) and show synergy of low dose of pipamperone and SSRI's. The results shown in the specification does not commensurate in scope of the claims.

Applicants' argue that that the use of daily low dose between 5- 15 mg of pipamperone augments the effect of SSRI in treating a disorder and Dipiperon document of record teaches away from that. In response, the claims of the instant

invention are directed towards a formulation and not to a method of treatment. The prior art including Dipiperon teaches a daily dose of 20 mg of Pipamperone administered to children. The instant claim teaches up to 15 mg of pipamperone. The amount of an ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. One of ordinary skill in the art would have been motivated to add less amounts of the drugs in combination in expectation of synergistic effects. It is also known in the art that in combination therapy or when two drugs used for the same purpose is combined a low dosage amount of either or both of the drugs in expectation of synergistic results. Dudley teaches both the compounds pipamperone and citalopram as antidepressants and it would have been obvious to one having ordinary skill in the art to try to combine them in a single pharmaceutical composition.

Applicants' arguments regarding the Dudley reference has been fully considered. Dudley reference has been cited to show that pipamperone and citalopram are known antidepressants in the art and furthermore, the reference teaches combining antidepressants in treating anti-depressive disorders. Hence one having ordinary skill in the art would have been motivated to combine drugs that are useful for the same treatment in expectation of success, in expectation of synergistic or additive therapeutic benefits.

Applicants' argue that Dudley does not teach any combination having a beneficiary effect. In response, Dudley teach both citalopram and pipamperone are antidepressants. Hence one having ordinary skill in the art would have been motivated

to combine drugs that are useful for the same treatment in expectation of success, in expectation of synergistic or additive therapeutic benefits. MPEP 2105 states: Evidence of similar properties or evidence of any useful properties disclosed in the prior art that would be expected to be shared by the claimed invention weighs in favor of a conclusion that the claimed invention would have been obvious. Dillon, 919 F.2d at 697-98, 16 USPQ2d at 1905; In re Wilder, 563 F.2d 457, 461,195 USPQ 426, 430 (CCPA 1977); In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972)

Applicants argue that Medicaments Psychotropes teaches a start dose of 10 mg and it is not the treatment dose and does not provide information on disorders or diseases that can be treated. In response, the document is cited to show that 10 mg initial dose is provided to children and the dosage is optimized based on other criteria. It is already known in the prior art that pipamperone is an antidepressant and has been shown to be an anti-psychotic agent. Dosage is clearly a result effective parameter that can be optimized. It is also known in the art that in combination therapy or when two drugs used for the same purpose is combined a low dosage amount of either or both of the drugs in expectation of synergistic results.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, the cited references teach both pipamperone and citalopram as antidepressants. Therefore, their combined teachings are not a case of improper hindsight, rather, *prima facia* obviousness.

Any rejection of record not addressed herein is withdrawn.

Conclusion

No claims are allowed.

Applicants' amendment necessitated the new and modified rejections presented in this action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Umamaheswari Ramachandran whose telephone

number is 571-272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617